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MAIN TEXT

Higher mean cerebral oxygen saturation shortly after extracorporeal cardiopulmonary resuscitation in patients who regain consciousness

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Abstract

Introduction: In cardiac arrest, cerebral ischemia and reperfusion injury mainly determine the neurological outcome. The aim of this study was to investigate the relation between the course of cerebral oxygenation and regain of consciousness in patients treated with extracorporeal cardiopulmonary resuscitation (ECPR). We hypothesized that rapid cerebral oxygenation increase causes unfavorable outcomes.

Methods: This prospective observational study was conducted in three European hospitals. We included adult ECPR patients between October 2018 and March 2020, in whom cerebral regional oxygen saturation (rSO_2) measurements were started minutes before ECPR initiation until 3 h after. The primary outcome was regain of consciousness, defined as following commands, analyzed using binary logistic regression.

Results: The sample consisted of 26 ECPR patients (23% women, Age_{mean} 46 years). We found no significant differences in rSO_2 values at baseline (49.1% versus 49.3% for regain versus no regain of consciousness). Mean cerebral rSO_2

values in the first 30 min after ECPR initiation were higher in patients who regained consciousness (38%) than in patients who did not regain consciousness (62%, odds ratio 1.23, 95% confidence interval 1.01–1.50).

Conclusion: Higher mean cerebral rSO_2 values in the first 30 min after initiation of ECPR were found in patients who regained consciousness.

KEYWORDS

cardiac arrest, cerebral regional oxygen saturation, ECPR, extracorporeal cardiopulmonary resuscitation, extracorporeal membrane oxygenation, heart arrest, near-infrared spectroscopy

1 | INTRODUCTION

Cerebral ischemia and reperfusion injury determine the neurological outcome in cardiac arrest patients. The extent of ischemic damage is highly influenced by the duration of cardiac arrest.[1] In order to shorten the ischemic period in patients with refractory cardiac arrest, extracorporeal cardiopulmonary resuscitation (ECPR) can be used. However, after restoration of circulation by either return of spontaneous circulation (ROSC) or initiation of ECPR, reperfusion injury can further add to the total amount of injury. A sudden restoration or overshoot of cerebral oxygen delivery after return of circulation causes hyperemia followed by hypoperfusion.[2] This results in endothelial dysfunction which causes a decrease in flow, resulting sometimes in a vicious circle of decreasing oxygen delivery and edema.[2]

After initiation of ECPR, hemodynamic parameters will restore rapidly, while effects on clinical outcomes are largely unknown.[3] Depending on extracorporeal membrane oxygenation (ECMO) settings in the initial phase of ECPR (i.e., FiO_2 in the oxygenator and ECMO blood flow and gas flow), arterial partial oxygen pressure (PaO_2), arterial partial carbon dioxide pressure ($PaCO_2$), and mean arterial pressure (MAP) can be largely and rapidly influenced. The effects of these rapid fluctuations in the direct post-resuscitation phase are unknown.[2] An experimental animal study showed that, especially early after initiation of ECPR, cardiac output, and MAP are higher in ECPR than in ROSC after conventional CPR (CCPR).[4] When comparing ECPR with a non-pulsatile blood flow and MAP 40–60 mmHg strategy to ECPR with a pulsatile blood flow and MAP 100–120 mmHg strategy, higher markers of cardiac injury and lower favorable neurological survival were found in the non-pulsatile group.[5]

Two meta-analyses and the first randomized controlled trial (RCT) showed higher rates of favorable neurological survival in ECPR than in CCPR-treated patients.[6–8] Despite these positive results, it is still unknown what the best treatment protocol of ECPR is in order to improve favorable neurological survival. Our hypothesis is that a rapid increase in cerebral regional oxygen saturation (rSO_2) could result in tissue damage, because of long duration of hypoxemia and high gradient after initiating ECPR. With this hypothesis, a slow rise of cerebral rSO_2 after initiation of ECPR may result in a better neurological recovery and outcomes. Therefore, the aim of this study was to investigate the relation between the course of cerebral oxygenation, measured with near-infrared spectroscopy (NIRS) in the first 3 h after initiation of ECPR, and regain of consciousness as intermediate endpoint of neurological outcome.

2 | MATERIALS AND METHODS

This prospective observational study (registered at clinicaltrials.gov: NCT03592810) was conducted in three European hospitals: IRCCS Policlinic Hospital San Matteo (HSM) Pavia (Italy), University Hospital Antwerp (UHA) (Belgium), and Erasmus University Medical Center (EMC) Rotterdam (The Netherlands). The Medical Ethics Committee of the EMC reviewed and approved the study protocol (MEC-2017-330), and this approval was confirmed locally at HSM and UHA. All surviving patients who participated in this study gave consent.

2.1 | Patients

From October 1, 2018, to March 1, 2020, all patients receiving ECPR were eligible to be included. We included adult patients with out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA), treated with ECPR (defined as initiation of venoarterial extracorporeal membrane oxygenation (VA-ECMO) during cardiopulmonary resuscitation (CPR)), in whom cerebral regional oxygen saturation (rSO_2) monitoring using NIRS was initiated before start of ECPR blood flow. Exclusion criteria for this study were as follows: ECPR patients without rSO_2 measurements before ECPR initiation, that is, baseline measurement, ROSC before ECPR flow, and tamponade,

hypothermia, or dissection as cause of arrest. The full list of in- and exclusion criteria for this study are shown in Supplementary Material, Table S1.

2.1.1 | ECPR procedure

When the decision for ECPR was made, ultrasound-guided, percutaneous cannulation was performed in the common femoral artery and vein. In case the ECPR procedure was executed in the operation room, a surgical procedure was performed (by a femoral cutdown). We used a 17–19 Fr arterial cannula and a 21–25 Fr venous cannula (Getinge group, Maquet HLS cannula). ECPR was initiated using the Cardiohelp system (Getinge group, Maquet Cardiopulmonary GmbH, Germany). After initiation of ECPR blood flow, an antegrade 6 Fr cannula was placed in the ipsilateral superficial femoral artery for antegrade leg perfusion. The amount of ECPR blood flow, gas flow, and supplied oxygen of the Cardiohelp (ECPR-FiO2) was left to the discretion of the attending physician. Decisions to withdraw life-sustaining therapy were based on national protocols in accordance with the ERC guidelines 2015.

2.2 | Study variables

The following variables were extracted from the patient records: patient characteristics, clinical characteristics, and clinical outcomes. *Patient characteristics* included gender, age at arrest, length, weight, acute physiology, and chronic health evaluation (APACHE) IV. *Clinical characteristics* included primary cardiac rhythm, location of arrest (OHCA/IHCA), pre-hospital duration, CPR delay (i.e., no-flow duration), total duration of CPR (i.e., low-flow duration, periods with ROSC excluded), duration from start CPR until initiation of ECPR (this included periods with ROSC), number of days on VA-ECMO, and cardiac or pulmonary history. *Clinical outcomes* included: complications: continuous renal replacement therapy (CRRT), bleeding (defined as bleeding in need of intervention or blood transfusion), intracranial bleeding, ECMO complications, length of stay, hospital survival, 6-month survival, Cerebral Performance Category (CPC)-score at hospital discharge, maximum Glasgow Coma Scale (GCS) during admission. Six months after ECPR initiation, we contacted the patients and took a questionnaire to determine the CPC score.[9] Our primary outcome was regain of consciousness defined as following commands at some point after ECPR initiation. We choose this as our primary outcome, because our aim was to study the effects of the course of oxygen in the cerebral tissues on the intermediate endpoint of neurological outcome. Patients treated with ECPR are one of the most critical patients admitted to the ICU and they are prone to developing many other complications during their admission. Many of them will most probably not be influenced by the oxygen level in the first hours after ECMO initiation. When patients had regain of consciousness, the oxygen delivery during ECPR should be considered adequate. As secondary outcomes, we reported hospital survival and favorable neurological survival (defined as CPC score 1–2) at 6 months after ECPR initiation.

2.3 | Measurements

When a potential ECPR procedure was announced, the local investigator was called. Before ECPR initiation the skin sensors were placed on the left and right side of the patient's forehead and cerebral rSO_2 measurements were started using the Sensmart (Model X-100, Nonin, Plymouth Minnesota, USA). To summarize the individual courses of the mean cerebral rSO_2, we defined and calculated the following five variables (Supplementary Material Figure S3) and compared them between ECPR patients who did and did not regain consciousness: (1) slope (i.e., rate of increase over time) of cerebral rSO_2 values in the first 30 min, (2) mean value over the first 30 min, (3) baseline cerebral rSO_2 measurements, (4) variability (i.e., standard deviation) of the cerebral rSO_2 from 30–180 min, and (5) mean value from 30 min until 180 min. To compare the cerebral rSO_2 measurements with outcomes, we calculated the mean cerebral rSO_2 by averaging the measurement from both sides. In case there was only one variable (left or right) available, we used the single measurement. The differences between left and right were plotted using the scatter plot and Bland–Altman plot for the total sample (Supplementary Material, Figure S1). Supplementary Material Figure S2 shows also the scatter plot and Bland–Altman plot only including data in the first 30 min after ECMO initiation. The outliers of these plots were mainly caused by one patient's measurements, who had a left–right difference most probably due to a subdural hematoma. Arterial blood gas analyses were performed every 15 min in the first hour, and every 30 min afterward until 3 h after ECPR initiation. Mean arterial pressure (MAP), ECPR blood flow, gas flow, and ECPR-FiO_2 were continuously monitored.

2.4 | Sample size

The pre-planned sample size was $N = 200$ patients in 18 months. The planned sample size was set based on the planned number of participating hospitals, including

$N = 20$ patients per center. There were 10 devices available to perform measurements in 10 participating hospitals. The estimated number of patients per participating hospital was based on the number of ECPR procedures performed in 18 months, excluding patients with ROSC pre-ECMO flow, missing cerebral oxygenation measurements, and cerebral oxygenation measurements not started in time.

2.5 | Statistical analysis

We used the Shapiro–Wilk test to assess whether continuous variables were normally distributed. In case of a normal distribution, we reported mean and standard deviation (SD); in case variables were not normally distributed, we reported median and interquartile ranges (IQR). Categorical variables were reported as numbers and percentages (%). In univariable analyses, ECPR patients with and without regain of consciousness of continuous variables were compared using independent sample t-tests for normally distributed variables and using Mann–Whitney U-tests for non-normally distributed variables. Statistical differences in categorical variables were tested using the chi-squared test (with >5 cases in each cell) or Fisher's exact test (with ≤5 cases in one of the cells).

Univariable logistic regression analyses were used to assess associations between these five variables describing the individual courses of mean cerebral rSO_2 (see measurements above) and the primary outcome, that is, regain of consciousness, and secondary outcomes, that is, hospital survival and favorable neurological survival at 6 months. We performed multivariable logistic regression analyses to assess associations between cerebral rSO_2, low-flow duration (as very important factor for regaining consciousness) and the primary outcome. Additionally, we performed these analyses for our secondary outcome. The correlation of ECMO blood flow and cerebral rSO_2 was tested using Pearson correlations and Bland–Altman plots. All statistical tests were two-sided with a significance level of 0.05. Data management and statistical analyses were performed in R, version 3.6.0.

3 | RESULTS

In this study period, 91 patients were eligible for an ECPR procedure. We included 26 patients in this study, five patients at HSM, 1 patient at UHA, and 20 patients at EMC. Reasons for exclusion of 65 patients are shown in Figure 1 and Supplementary Material Appendix S1. Two patients had an atypical age of 17 and 77 years; nevertheless, we decided to include their data. Of all included patients, 10 (38%) regained consciousness after ECPR initiation (at any time from initiation of ECPR until 6-month follow-up).

3.1 | Patient and clinical characteristics

As shown in Table 1, the mean age was 46 years (SD 15 years) and six (23%) patients were women. Clinical characteristics are shown in Table 1. A shockable primary cardiac rhythm was present in eight (31%) patients, pulseless electrical activity (PEA) in 13 (50%) patients, and asystole in five (19%) patients. The majority of the patients suffered from an OHCA ($N = 22$, 85%) and the mean total CPR time was 68 min (SD 25 min), 56 min in patients who regained consciousness and 75 min in patients who did not regain consciousness ($p = 0.05$). The baseline rSO_2 was 49% (SD 7%), the baseline mean PaO_2 was 8.9 kPa (SD 1.9 kPa), mean arterial saturation at baseline was 67% (SD 13%), and the baseline mean lactate value was 14.1 mmol/L (SD 4.0 mmol/L). After 3 h of ECPR PaO_2 values were 14.6 kPa (IQR 11.8–20.9 kPa), saturation was 96% (90–98%), and lactate 9.7 mmol/L (4.7 mmol/L). Patients who regained consciousness had a statistically significant higher ECMO blood flow in the first 3 h after initiation. All other patient and clinical characteristics did not show statistically significant differences. In Supplementary Material Table S2, the patient and clinical characteristics of the patients with long-term favorable neurological survival are shown.

3.2 | Primary outcome

As for the primary outcome, regain of consciousness, five variables of the course of cerebral rSO_2 were studied, as shown in Tables 2 and 3. The slope of rSO_2 in the first 30 min after ECPR initiation did not show a statistically significant difference for patients with and without regain of consciousness. Patients who regained consciousness had higher mean cerebral rSO_2 in the first 30 min than patients who had no regain of consciousness. This mean cerebral rSO_2 in the first 30 min was 69% (SD 3%) for patients who regained consciousness and 62% (SD 7%) for patients who had no regain of consciousness (OR 1.26 per % rSO_2 increase, 95% CI 1.03–1.53). Baseline rSO_2 values, before initiation of ECPR, did not differ between patients who regained consciousness and those who did not (mean 49%). The ECMO blood flow was not correlated with cerebral rSO_2, neither for the first 30 min nor for the first 3 h ($r = 0.31$, $p = 0.14$ and $r = 0.25$, $p = 0.22$, respectively). The ECMO blood flow and gas flow levels for every 5 min in the first 30 min stratified by regain of consciousness are presented in Supplementary Material Table S3.

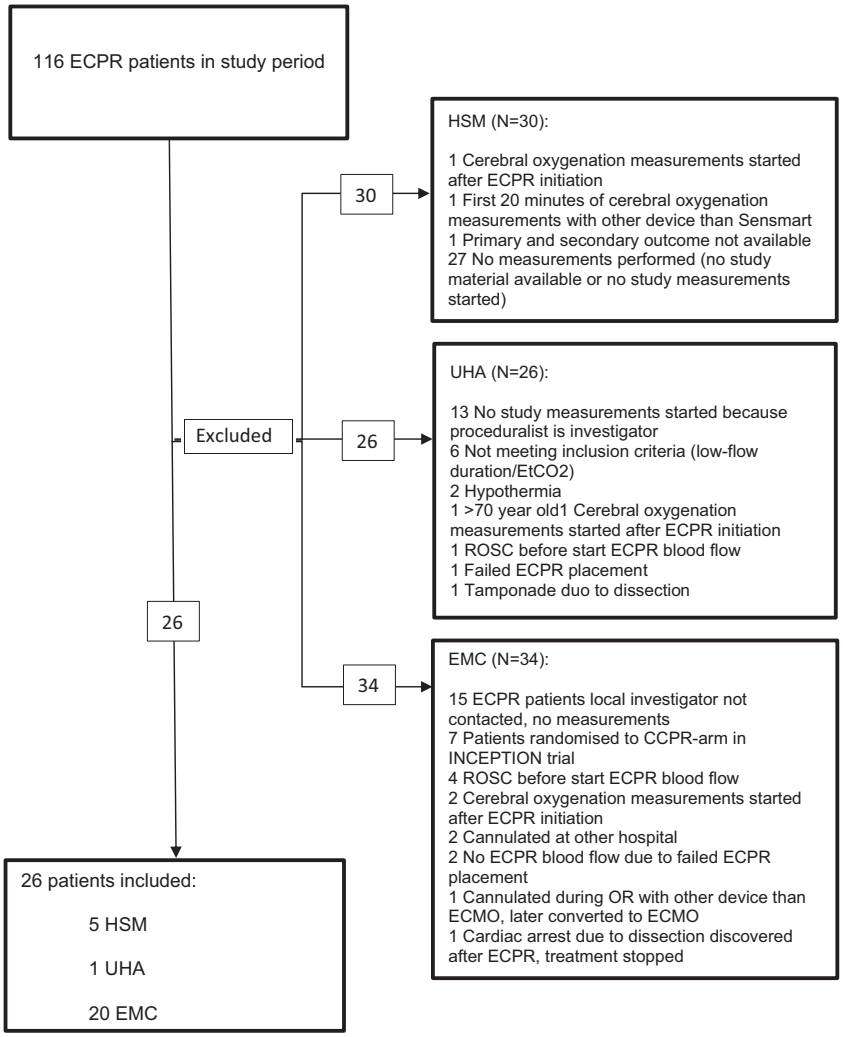

FIGURE 1 Flow chart of included and excluded patients. CCPR, conventional cardiopulmonary resuscitation; EMC, Erasmus University Medical Center; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; HSM, Hospital San Matteo; ROSC, return of spontaneous circulation; UHA, University Hospital Antwerp.

For the multivariable analysis, we included only two variables, mean cerebral rSO_2 in the first 30 min and low-flow duration in minutes. We decided to adjust for the component which probably influenced the outcome most, namely the low-flow duration. This analysis is shown in Table 3 where we demonstrate that the mean cerebral rSO_2 in the 30 min remained significantly higher in patients who regained consciousness (OR 1.23 per % rSO_2 increase, 95% CI 1.01–1.50) after adjustment for low-flow duration. The course of median rSO_2 of patients who regained consciousness versus those who had no regain of consciousness are shown in Figures 2 and 3.

3.3 | Secondary outcomes

Eight (31%) patients survived until hospital discharge, of which seven (88%) patients regained consciousness. Five (24%) patients had a CPC score of 1–2 at 6 months, one patient had a CPC score of 3, and two patients died in the following 6 months after hospital discharge. The course of cerebral rSO_2 was not significantly correlated to hospital survival as shown in the univariable and multivariable analyses in Supplementary Material Table S4.

Six (23%) patients were alive at 6 months after ECPR initiation. Of those one (4%) patient had a CPC score of 1, four (15%) patients had a CPC score of 2, and one (4%) patient had a CPC score of 3. In Supplementary Material Table S2 the outcomes are shown based on favorable neurological survival at 6 months after ECPR initiation. As shown in Table 4 and Supplementary Material Table S5, the course of cerebral rSO_2 was not significantly correlated to favorable neurological survival at 6 months as shown in the univariable and multivariable analyses. However, the number of patients which did reach the favorable neurological survival at 6 months was only five and therefore the non-significant outcome could be influenced by the sample size.

3.4 | Other outcomes

The short-term and long-term clinical outcomes are presented in Table 5. Complications were present in 21 (81%)

TABLE 1 Patient and clinical characteristics.

	Total	Regain of consciousness	No regain of consciousness	
	N = 26	*N* = 10	*N* = 16	*p*-value
Age (years)	46 (15)	45 (19)	48 (12)	0.66
Women (%)	6 (23%)	2 (20%)	4 (25%)	1.00
BMI (kg/m^2)	29.4 (6.3)	28.7 (6.7)	29.9 (6.2)	0.64
APACHEIV	124 (91–134)	109 (35)	117 (33)	0.57
Cardiac characteristics				
Primary cardiac rhythm (%)				0.16
VF/VT	8 (31%)	4 (40%)	4 (25%)	
PEA	13 (50%)	6 (60%)	7 (44%)	
Asystole	5 (19%)	0 (0%)	5 (31%)	
OHCA (%)	22 (85%)	7 (70%)	15 (94%)	0.26
Witnessed arrest (%)[a]	24 (92%)	9 (90%)	15 (94%)	1.00
Signs of life during CPR (e.g., gasping, movement) (%)[a]	4 (15%)	3 (30%)	1 (6%)	0.26
BLS or ALS in case of EMS witnessed arrest (%)	26 (100%)	10 (100%)	16 (100%)	
Pre-hospital time (minutes)	38 (20)	36 (16)	39 (22)	0.76
CPR delay (minutes)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.5)	0.63
Low-flow-duration (minutes)	68 (25)	56 (20)	75 (26)	0.05
Time CPR to ECPR (minutes)	71 (26)	61 (26)	77 (26)	0.15
ECMO characteristics				
ECMO blood flow 0–30 min	3.5 (3.4–3.8)	3.7 (3.5–4.0)	3.5 (3.2–3.6)	0.09
ECMO gas flow 0–30 min	2.1 (2.0–2.6)	2.0 (2.0–2.2)	2.4 (2.0–2.6)	0.36
ECMO blood flow 0–180 min	3.5 (0.7)	3.8 (0.5)	3.3 (0.7)	**0.04**
ECMO gas flow 0–180 min	2.5 (0.8)	2.3 (0.6)	2.6 (0.9)	0.31
Laboratory values				
Baseline				
pH	6.77 (6.75–6.83)	6.75 (6.75–6.75)	6.81 (6.78–6.91)	0.22
$PaCO_2$ (kPa)	9.9 (2.9)	11.4 (4.2)	9.2 (2.5)	0.60
PaO_2 (kPa)	8.9 (1.9)	10.0 (3.2)	8.3 (1.3)	0.60
Saturation (%)	67 (13)	68 (21)	67 (12)	0.95
Lactate (mmol/L)	14.1 (4.0)	17.5 (0.7)	12.4 (3.8)	0.07
After 3 h ECPR				
pH	7.07 (0.16)	7.13 (0.13)	7.01 (0.16)	0.08
$PaCO_2$ (kPa)	5.9 (5.2–6.9)	6.2 (5.9–7.3)	5.3 (5.0–6.0)	0.06
PaO_2 (kPa)	14.6 (11.8–20.9)	17.1 (13.7–21.0)	20.1 (10.7–19.3)	0.49
Saturation (%)	96 (90–98)	98 (96–99)	95 (85–97)	0.14
Lactate (mmol/L)	9.7 (4.7)	9.1 (5.2)	10.2 (4.4)	0.60

Abbreviations: ALS, advanced life support; APACHE IV, acute physiology and chronic health evaluation IV; BLS, basic live support; BMI, body mass index; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; EMS, emergency medical service; OHCA, out-of-hospital cardiac arrest; $PaCO_2$, partial carbon dioxide pressure; PaO_2, partial oxygen pressure; PEA, pulseless electrical activity; VF/VT, ventricular fibrillation/ventricular tachycardia.

[a]In two patients, there was a witnessed arrest and signs of life, in five patients the data of signs of life was missing (they all had witnessed arrests).

patients: eight (30%) patients required CRRT for acute kidney injury, 11 (41%) patients had a bleeding, and five (19%) patients had extracorporeal membrane oxygenation (ECMO) related complications. These ECMO-related complications and associated treatments are provided in Supplementary Material Table S6. The reasons for

TABLE 2 Cerebral rSO_2 variables.

Slope cerebral rSO_2 first 30 min	0.43 (0.43)	0.41 (0.39)	0.44 (0.47)	0.87
Mean cerebral rSO_2 0–30 min (%)	64.7 (7.0)	69.2 (3.2)	61.8 (7.3)	**<0.01**
Baseline cerebral rSO_2 (%)	49.3 (7.1)	49.1 (5.5)	49.3 (8.1)	0.93
Standard deviation cerebral rSO_2 30–180 min (%)	3.6 (2.5–4.7)	3.8 (2.9–4.6)	3.6 (2.3–4.5)	0.39
Mean cerebral rSO_2 30–180 min (%)	70.0 (7.1)	71.4 (3.9)	69.1 (8.5)	0.37

Abbreviation: rSO_2, regional oxygen saturation.

TABLE 3 Univariable and multivariable logistic regression analyses of the course of cerebral rSO_2 for regain of consciousness.

	OR (95% CI)
Univariable logistic regression analyses	
Slope cerebral rSO_2 30 min	0.851 (0.133–5.445)
Mean cerebral rSO_2 30 min	1.255 (1.030–1.530)
Baseline cerebral rSO_2	0.995 (0.889–1.114)
Standard deviation cerebral rSO_2 30–180 min	0.986 (0.696–1.396)
Mean cerebral rSO_2 30–180 min	1.050 (0.930–1.184)
Multivariable logistic regression analysis	
Low-flow duration	0.957 (0.906–1.011)
Mean cerebral rSO_2 30 min	1.233 (1.011–1.503)

Abbreviations: OR, odds ratio; rSO_2, regional oxygen saturation.

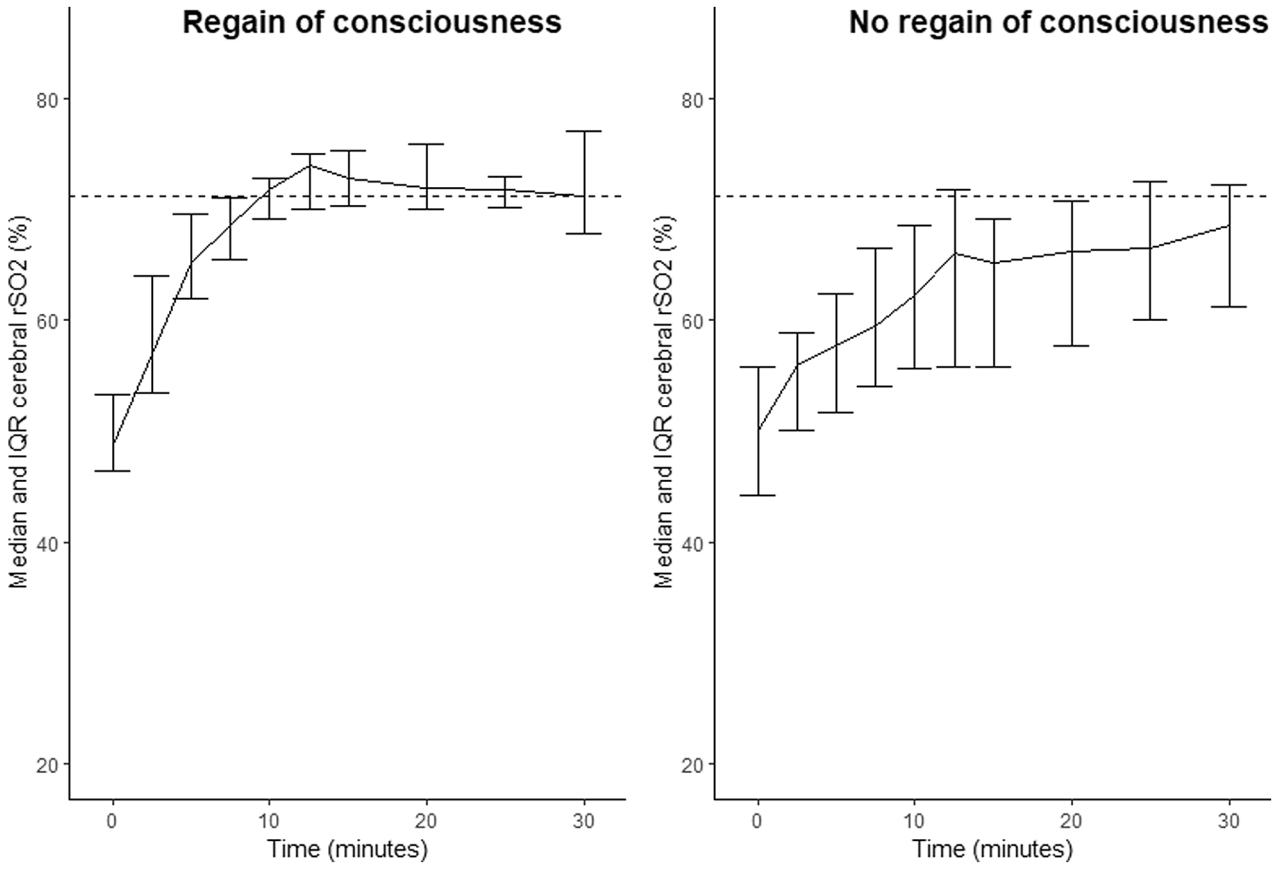

FIGURE 2 Course of cerebral rSO_2 in the first 30 min after ECPR initiation for patients with and without regain of consciousness. Median values (continuous line) and IQRs (vertical lines) of the two patient groups over time. Dashed line is rSO_2 value of healthy volunteers published by Ehara et al.[10] IQR, interquartile range; rSO_2, regional oxygen saturation.

initiation of ECPR and the cause of death are presented in Supplementary Material, Table S7. Five patients did not receive an interruption or cessation of sedation after ECPR, because of the rapid worsening of hemodynamic/neurological condition and withdrawal of life-supporting treatment before a wakeup call was performed. The cause of death of patients with and without an interruption or cessation of sedation is presented in Supplementary Material, Table S8.

4 | DISCUSSION

In this study, we found that patients who regained consciousness had statistically significant higher mean cerebral rSO_2 values in the first 30 min after initiation of ECPR than patients who did not regain consciousness even after adjustment for low-flow duration. In this study, 38% of the patients regained consciousness. Furthermore, we found a hospital survival rate of 31% and a 6-month favorable neurological survival rate of 24%.

Higher cerebral rSO_2 values in the first 30 min of ECPR were associated with neurological recovery, even after adjusting for low-flow-duration. Our study shows that after initiation of ECPR, cerebral rSO_2 values rise directly. Yagi et al[11] also showed a significant rise in rSO_2 after initiation of ECPR. Other studies studying the relation of initiation of ECPR and the direct effect on cerebral rSO_2 in ECPR are limited. Luo et al[12] showed in an experimental study that a higher tissue oxygenation was associated with higher ECMO blood flow in ECPR. This is similar to our result that patients who regained consciousness had higher ECMO blood flows. Higher cerebral oxygenation values caused by starting ECMO flow will provide the cells enough oxygen to restart cellular processes and ATP production as soon as possible.

In our study, the baseline cerebral rSO_2 did not influence the regain of consciousness. In other experiences as Ehara et al,[10] showed that patients with favorable neurological survival had higher rSO_2 values before initiation of ECPR than patients without favorable neurological survival. Tsukuda et al,[13] also showed that baseline cerebral rSO_2 influenced the outcome in cardiac arrest patients. In these two studies, the baseline cerebral rSO_2 values during cardiac arrest were higher in the patients who had favorable outcomes.

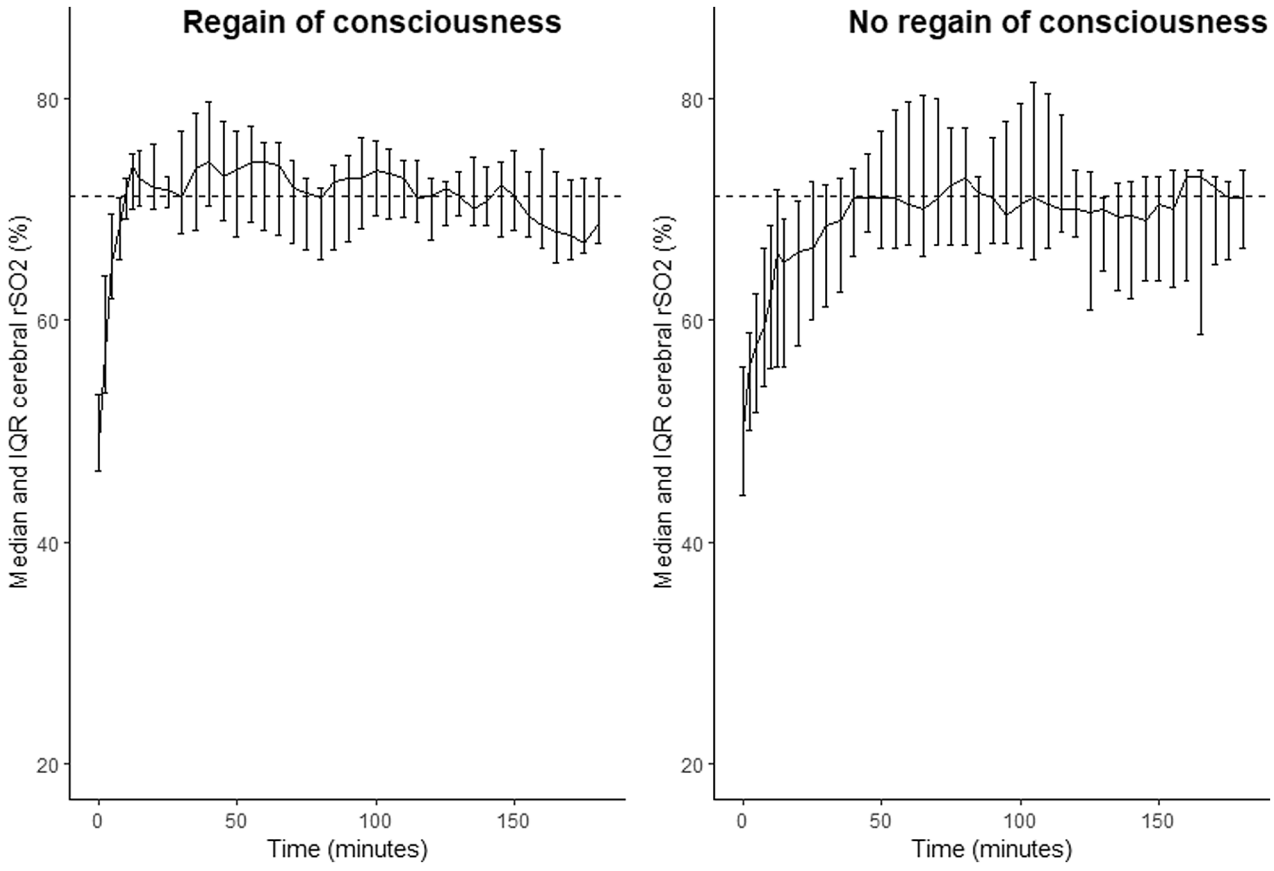

FIGURE 3 Course of cerebral rSO_2 in the first 3 h after ECPR initiation for patients with and without regain of consciousness. Median values (continuous line) and IQRs (vertical lines) of the two patient groups over time. Dashed line is rSO_2 value of healthy volunteers published by Ehara et al.[10] IQR, interquartile range; rSO_2, regional oxygen saturation.

Our hypothesis that a slow rise of cerebral rSO_2 after initiation of ECPR would result in a better neurological recovery, was not supported by this study. A rapid increase in oxygen delivery might increase reperfusion injury by the toxic effect of hyperoxemia. In the study by Ehara et al,[10] patients with favorable neurological survival had no significant increase in rSO_2 after ECPR initiation, while patients without favorable neurological survival did. In our study as well as previous studies, it is not completely clear if the rSO_2 levels during CPR could be influenced by cerebral cell damage, especially in patients who die in a short period after ECPR initiation. Also, recovering macrocirculatory flow by using ECMO may not result in recovering microcirculatory flow, especially shortly after initiation.[12,14] Despite the attempt of to find a relation between the course of rSO_2 and neurological recovery, the exact relation still remains unclear.

Extracorporeal cardiopulmonary resuscitation is used as a treatment modality which, by oxygenating vital organs as soon as possible, buys time to resolve the problem which caused the cardiac arrest. Neurological recovery was present in 38% of the patients included in this study. Kobota et al[15] found regain of consciousness in 20% of the included patients, somewhat lower than

TABLE 4 Multivariable logistic regression analyses of the course of cerebral rSO_2 for favorable neurological outcome.

Multivariable	OR (95% CI)
Low-flow duration	0.884 (0.723–1.079)
Mean cerebral rSO_2 30 min	1.261 (0.965–1.650)

Abbreviations: OR, odds ratio; rSO_2, regional oxygen saturation.

TABLE 5 Outcomes.

	Total	Regain of consciousness	No regain of consciousness	
	$N=26$	$N=10$	$N=16$	p-value
No. of ECMO days (days)	2 (1–4)	4 (2–6)	1 (1–2)	**<0.01**
Complications (%)	21 (81%)	10 (100%)	11 (69%)	0.12
CRRT	8 (30%)	4 (40%)	4 (29%)	0.67
Bleeding	11 (41%)	6 (60%)	5 (45%)	0.67
Cerebral bleeding	1 (4%)	1 (10%)	0 (0%)	0.48
ECMO-related Complication	5 (19%)	1 (10%)	4 (36%)	0.31
Maximum GCS	3.0 (3.0–11.8)	13.5 (11.3–15.0)	3.0 (3.0–3.0)	**<0.01**
Length of stay ICU (days)	2 (1–11)	12 (5–18)	1 (1–2)	**<0.01**
Days until death (days)	2 (1–4)	13 (6–21)	1 (1–2)	**<0.01**
ICU survival (%)	9 (35%)	8 (80%)	1 (6%)	**<0.01**
Hospital survival (%)	8 (31%)	7 (70%)	1 (6%)	**<0.01**
6-month survival (%)	6 (23%)	6 (60%)	0 (0%)	**<0.01**
CPC score at hospital discharge (%) missing $n=1$				
1	0 (0%)	0 (0%)	0 (0%)	
2	2 (8%)	2 (20%)	0 (0%)	
3	5 (19%)	5 (50%)	0 (0%)	
4	0 (0%)	0 (0%)	0 (0%)	
5	18 (73%)	3 (30%)	15 (94%)	
CPC score at 6-months (%) died within 6 months, $n=2$				
1	1 (4%)	1 (10%)	0 (0%)	
2	4 (15%)	4 (40%)	0 (0%)	
3	1 (4%)	1 (10%)	0 (0%)	
4	0 (0%)	0 (0%)	0 (0%)	
5	20 (77%)	4 (40%)	16 (100%)	

Note: Total CPR time was defined as time the patient needs compressions, time periods of return of spontaneous circulation (ROSC) excluded. Time CPR to ECPR is defined as time between start of CPR and start of ECMO blood flow.

Abbreviations: CPC, cerebral performance category; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation; GCS, Glasgow Coma Scale; ICU, intensive care unit.

in our sample. In a study by Trummer et al,[16] regain of consciousness was found in even 50% of the ECPR-treated patients. They applied a treatment modality in which the ECPR treatment was more individually based, which could explain the difference with our outcomes. Yannopoulos et al,[8] found in their RCT 6-month favorable neurological survival of 43%. The high long-term survival could be explained by a difference in experience with ECPR initiation and ECPR treatment, a difference in inclusion criteria, or differences in pre-hospital management or post-cardiac arrest care.

Our study had several limitations. The number of included patients was lower than the number of eligible ECPR patient in the study period. An ECPR procedure remains a stressful situation, in which placement of sensors for this study could easily be forgotten and dedicated research staff at all times during the week was missing. This results in the fact that only patients in whom measurements were performed in time were included in this study. Our initial aim was to include a total of 200 patients in 10 hospitals. Unfortunately, we did not reach this number of participating hospitals due to several factors (e.g., no agreement of head of department for starting the study, delay in receiving study materials of supplier, wasting of study materials by starting measurements too late, patients not treated with ECPR due to randomization into the CCPR group of the INCEPTION study[17]). In the three hospitals that did participate, we included a lower number of patients than expected. As a consequence, we were unable to correct for more than two variables in the multivariable analysis. This limits the statistical power and generalizability of the study. Also, in some patients treatment was stopped before regaining of consciousness could be tested, due to clinical deterioration on ECMO, these patients were scored as no regain of consciousness. Furthermore, we intended to include the mean arterial pressure for every 5 min in the first 30 min after ECMO initiation. However, because this was mostly during transportation of the patient from the Emergency Department to the Intensive Care Unit, these values were largely missing in the patient record. Therefore, we decided to exclude this parameter.

To get more insight into the effect of cerebral rSO_2, a randomized controlled trial in which several treatment options are compared, would be very informative. Future studies should still focus on determining the ideal ECPR settings for reaching the best possible outcomes. Cerebral rSO_2 measurements could be useful to determine whether ischemic injury (which could be represented as baseline rSO_2 and mean rSO_2) or reperfusion injury (which could be represented as slope and course of rSO_2) is the most important factor in determining neurological outcome. Larger samples, and preferably randomized controlled settings, are important to expand the existing knowledge of this promising treatment.

5 | CONCLUSION

Higher mean cerebral rSO2 values in the first 30 min after initiation of ECPR were found in patients who regained consciousness.

AUTHOR CONTRIBUTIONS

LM contributed to the acquisition of data, analysis, and interpretation of data, writing original draft and revising it, final approval, and submission. CU, JR, and WR contributed to the analysis and interpretation of data, critical revision of article, and final approval, MB and RT contributed to the conception and design of the study, critical revision of article, and final approval. HR contributed to the conception and design of the study, revision of article, and final approval. ER and JM contributed to the acquisition of data, revision of article, and final approval. DM contributed to the conception and design of the study, analysis, and interpretation of data, critical revision of article, and final approval.

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CONFLICT OF INTEREST STATEMENT

DRM declares having received speaker fees from Xenios GmbH and HillRom GmbH. MB is a member of the medical advisory board of Eurosets srl (Medolla, Italy) and congress speaker for Hamilton Medical (Bonaduz, Swiss). DG is a member of the medical advisory board of Xenios GmbH and received travel expenses and speaker fees from Xenios and Maquet GmbH.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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